What is claimed is:

1. A compound having the formula:

H1 - X - B - Y - H2

wherein each of H1 and H2 may be the same or different and capable of binding to a receptor which is the same or different;

wherein each of X and Y may be present or absent and, if present, each may be the same or different spacer moiety;

wherein B is an enzyme-cleavable moiety.

2. The compound of claim 1, wherein each of H1 and H2 is capable of binding to a receptor with a IC_{50} of less than 100 nM.

3. The compound of claim 2, wherein each of H1 and H2 is capable of binding to a receptor with a IC_{50} of less than 10 nM.

4. The compound of claim 3, wherein each of H1 and H2 is capable of binding to a receptor with a IC_{50} of less than 1 nM.

5. The compound of claim 1, wherein B is capable of binding to an enzyme with an IC_{50} of less than 100 mM.

6. The compound of claim 5, wherein B is capable of binding to an enzyme with an IC_{50} of less than 10 mM.

7. The compound of claim 6, wherein B is capable of binding to an enzyme with an IC_{50} of less than 1 mM.

8. The compound of claim 1, wherein B is capable of binding to an enzyme with an IC_{50} of less than 100 μM.

9. The compound of claim 5, wherein B is capable of binding to an enzyme with an IC_{50} of less than 10 μM.

10. The compound of claim 6, wherein B is capable of binding to an enzyme with an IC_{50} of less than 1 μM.

11. The compound of claim 1, wherein H1 and H2 are different.

12. The compound of claim 1, wherein X and Y are different.

13. The compound of claim 1, wherein B is cleavable by an enzyme selected from the group of enzymes consisting of transferases, hydrolases, lyases, isomerases, and ligases.

14. The compound of claim 13, wherein the transferase is selected from the group consisting of, a carbon transferase, an aldehyde or ketone transferase, an acyl transferase, a glycosyl transferase, an alkyl or aryl trasferase, a N-containing group transferase, a P-containing group transferase, an S-containing group transferase, an O-containing group transferase, and a Se-containing group transferase.

15. The compound of claim 13, wherein the hydrolase is selected from the group consisting of an ester hydrolase, a glycosidic hydrolase, an ether hydrolase, a peptide hydrolase, a C-N (non-peptide) hydrolase, an acid anhydride hydrolase, a C-C hydrolase, a P-N hydrolase, an S-N hydrolase, a C-P hydrolase, C-O hydrolase (non-ester, non-ether), and an S-S hydrolase.

16. The compound of claim 13, wherein the lyase is selected from the group consisting of a C-C lyase, a C-O lyase, a C-N lyase, a C-S lyase, and a P-O lyase.

17. The compound of claim 13, wherein the isomerase is selected from the group consisting of racemases, epimerases, cis-trans isomerases, intra-oxidoreductases, intra-transferases (mutases), and intramolecular lyases.

18. The compound of claim 13, wherein the ligase is selected from the group consisting of a C-O ligase, a C-S ligase, a C-N ligase, a C-C ligase, and a P-O ligase.

19. The compound of claim 1, wherein B is an enzyme cleavable moiety selected from the group consisting of phosphodiester, glycoside, amide, ester, diester, and aldol product moiety.

20. The compound of claim 19, wherein B represents an amide moiety.

21. The compound of claim 20, wherein B represents a cephem moiety.

22. The compound of claim 1, wherein H1 or H2 is derived from a compound selected from the group consisting of steroids, hormones, nuclear receptor ligands, cofactors, antibiotics, sugars, enzyme inhibitors, and drugs.

23. The compound of claim 22, wherein H1 or H2 represents a compound selected from the group consisting of dexamethasone, 3,5,3'-triiodothyronine, *trans*-retinoic acid, biotin, coumermycin, tetracycline, lactose,

methotrexate, FK506, and FK506 analogs.

24. The compound of claim 23, wherein H1 or H2 is derived from the compound of Figure 5A.

25. The compound of claim 23, wherein H1 or H2 is derived from the compound of Figure 5B.

26. The compound of claim 23, wherein H1 or H2 is derived from the compound of Figure 5C.

27. The compound of claim 1, formed by reacting a first compound having the formula:

H1-X-B'

with a second compound having the formula:

H2-Y-B''

wherein B' and B'' are moieties that react to form B in the presence of an enzyme.

28. The compound of claim 27, wherein the enzyme is selected from the group of enzymes consisting of transferases, lyases, isomerases, and ligases.

29. The compound of claim 28, wherein the transferase is selected from the group consisting of, a carbon transferase, an aldehyde or ketone transferase, an acyl transferase, a glycosyl transferase, an alkyl or aryl trasferase, a N-containing group transferase, a P-containing group transferase, an S-containing group transferase, an O-containing group transferase, and a Se-containing group transferase.

30. The compound of claim 28, wherein the lyase is selected from the group consisting of a C-C lyase, a C-O lyase, a C-N lyase, a C-S lyase, and a P-O lyase.

31. The compound of claim 28, wherein the isomerase is selected from the group consisting of racemases, epimerases, cis-trans isomerases, intra-oxidoreductases, intra-transferases (mutases), and intramolecular lyases.

32. The compound of claim 28, wherein the ligase is selected from the group consisting of a C-O ligase, a C-S ligase,

a C-N ligase, a C-C ligase, and a P-O ligase.

33. A compound having the formula:

H1-X-B′

wherein H1 is capable of binding to a receptor;

wherein X is a spacer moiety which may be present or absent; and

wherein B′ is a moiety capable of binding to an enzyme.

34. The compound of claim 33, wherein H1 is capable of binding to a receptor with a IC_{50} of less than 100 nM.

35. The compound of claim 34, wherein H1 is capable of binding to a receptor with a IC_{50} of less than 10 nM.

36. The compound of claim 35, wherein H1 is capable of binding to a receptor with a IC_{50} of less than 1 nM.

37. The compound of claim 33, wherein B′ is capable of binding to an enzyme with an IC_{50} of less than 100 mM.

38. The compound of claim 37, wherein B′ is capable of binding to an enzyme with an IC_{50} of less than 50 mM.

39. The compound of claim 38, wherein B′ is capable of binding to an enzyme with an IC_{50} of less than 1 mM.

40. The compound of claim 39, wherein B′ is capable of binding to an enzyme with an IC_{50} of less than 100 μM.

41. The compound of claim 40, wherein B′ is capable of binding

to an enzyme with an IC_{50} of less than 10 μM.

42. The compound of claim 41, wherein B' is capable of binding to an enzyme with an IC_{50} of less than 1 μM.

43. The compound of claim 33, further capable of reacting with a moiety that has the formula:

H2-Y-B''

wherein H2 is capable of binding to a receptor;

wherein Y is a spacer moiety which may be present or absent; and

wherein B'' is a moiety that reacts with B' in the presence of the enzyme.

44. A complex comprising the compound of claim 1 complexed to an enzyme.

45. The complex of claim 44, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 100 mM.

46. The complex of claim 44, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 10 mM.

47. The complex of claim 44, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 1 mM.

48. The complex of claim 44, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 100 μM.

49. The complex of claim 44, wherein the compound is capable

of binding to the enzyme with an IC_{50} of less than 10 μM.

50. The complex of claim 44, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 1 μM.

51. A complex comprising the compound of claim 33 complexed to an enzyme.

52. The complex of claim 51, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 100 mM.

53. The complex of claim 51, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 10 mM.

54. The complex of claim 51, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 1 mM.

55. The complex of claim 51, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 100 μM.

56. The complex of claim 51, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 10 μM.

57. The complex of claim 51, wherein the compound is capable of binding to the enzyme with an IC_{50} of less than 1 μM.

58. A composition comprising the compound of claim 1, and the compound of claim 33.

59. The composition of claim 58, further comprising an enzyme.

60. A composition comprising the complex of claim 44.

61. A composition comprising the complex of claim 51.

62. A method of screening proteins for the ability to catalyze bond cleavage, comprising the steps of:

a) providing a cell that expresses a pair of fusion proteins which upon dimerization change a cellular readout;

b) providing a compound which dimerizes the pair of fusion proteins, said compound comprising two portions coupled by a bond that is cleavable by the protein to be screened; and

c) screening for the cellular readout, wherein a change in the cellular readout indicates catalysis of bond cleavage by the protein to be screened.

63. The method claim 62, wherein the cellular readout is reconstitution of enzymatic activity.

64. The method of claim 62, further comprising providing a cell that contains a gene which is activated by the dimerized pair of fusion proteins.

65. The method of claim 64, wherein the cellular readout is gene transcription, such that a decrease of gene transcripton indicates catalysis of bond cleavage by the protein to be screened.

66. The method of claim 65, wherein the gene transcribed is *lacZ, leu2, ura3, his3, or trp.*

67. The method of claim 62, wherein the compound which dimerizes the pair of fusion proteins is the compound of claim 1.

68. The method of claim 62, wherein the compound which dimerizes the pair of fusion proteins is the compound of claim 43.

69. A method of screening proteins for the ability to catalyze bond formation, comprising the steps of:

a) providing a cell that expresses a pair of fusion proteins which upon dimerization activate a cellular readout:

b) providing a first compound and a second compound, each being capable of binding to one of the pair of fusion proteins, said first and second compound comprising a portion through which the first and second compounds are coupled by the action of the bond forming protein to be screened; and

c) screening for the cellular readout, wherein a change in the cellular readout indicates catalysis of bond formation by the protein to be screened.

70. The method of claim 69, wherein the cellular readout is enzyme activity.

71. The method of claim 69, further comprising providing a cell that contains a gene which is activated by the dimerized pair of fusion proteins.

72. The method of claim 69, wherein the cellular readout is gene transcription, such that an increase in gene transcription indicates catalysis of bond formation by the protein to be screened.

73. The method of claim 69, wherein either the first or the second compound is the compound of claim 23.

74. The method of claim 62 or 69, wherein the cell is selected from the group consisting of yeast, bacteria or mammalian.

75. The method of claim 62 or 69, wherein the cell is selected from the group consisting of *S. cerevisiae*, and *E. coli*.

76. The method of claim 62 or 69, wherein the pair of fusion proteins is the hormone binding domain of the rat glucocorticoid receptor (rGR2) fused to *LexA*, and FKBP12 fused to the B42 transcriptional activation domain.

77. The method of claim 62 or 69, wherein the pair of fusion proteins is dihydrofolate reductase (DHFR) fused to *LexA*, and FKBP12 fused to the B42 transcriptional activation domain.

78. The method of claim 62 or 69, wherein the pair of fusion proteins is dihydrofolate reductase (DHFR) fused to *LexA*, and the rat glucocorticoid receptor (rGR2) fused to the B42 transcriptional activation domain.

79. The method of claim 62 or 69, wherein the pair of fusion proteins is the rat glucocorticoid receptor (rGR2) fused to *LexA*, and the hormone binding domain of dihydrofolate reductase (DHFR) fused to the B42 transcriptional activation domain.

80. The method of claim 62 or 69, wherein the pair of fusion proteins is dihydrofolate reductase (DHFR) fused to *LexA*, and the hormone binding domain of the rat glucocorticoid receptor (rGR2) fused through a 6-Glycine linker to the B42 transcriptional activation domain.

81. The method of claim 62 or 69, wherein the protein to be screened is an enzyme selected from the group of enzyme

classes consisting of transferases, hydrolases, lyases, isomerases and ligases.

82. The method of claim 62 or 69, wherein the screening is performed by Fluorescence Activated Cell Sorting (FACS), or gene transcription markers selected from the group consisting of Green Fluorescence Protein, *Lac*Z-β-galagctosidases, luciferase, antibiotic resistant β-lactamases, and yeast markers.

83. A method of screening a compound for the ability to inhibit an enzyme comprising:

screening for activity of the enzyme by the method of claim 62 or 69, and obtaining cells which express an active enzyme, and

contacting the cells with the drug to be screened, wherein a change in the transcription of the reporter gene within the cell after contact with the drug indicates inhibition of the enzyme by the drug.

84. A drug for the inhibition of an enzyme selected by the method of claim 83.

85. A method of evolving a protein with a new catalytic activity comprising screening by the method of claim 62 or 69 proteins derived from a library of proteins which are mutants of a known protein.

86. A protein with new catalytic activity evolved by the method of claim 85.

87. A method of evolving an enzyme with a new substrate

specificity comprising screening by the method of claim 62 or 69 enzymes derived from a library of enzymes which are mutants of an enzyme with known substrate specificity.

88. An engineered enzyme having new substrate specificity evolved by the method of claim 87.

89. A method for evolving an enzyme that functions with a cofactor which is different from the cofactor the natural coenzyme uses, comprising:

evolving mutants of the natural coenzyme; and

screening the mutants of the natural coenzyme by the method of claim 62 or 69 in the presence of a cofactor different from the cofactor of the natural enzyme.

90. An engineered enzyme that functions with a cofactor which is different from cofactors the enzymes naturally uses evolved by the method of claim 89.

91. A compound having the formula:

H1-Y-H2

wherein H1 is methorexate or an analog thereof;

wherein H2 is capable of binding to a receptor, and

wherein Y is a moiety providing a covalent linkage between H1 and H2, which may be present or absent, and when absent, H1 is covalently linked to H2.

92. The compound of claim 91, wherein H2 is Dex or an analog thereof.

93. The compound of claim 91, wherein H1 is Mtx and H2 is Dex or an analog thereof.

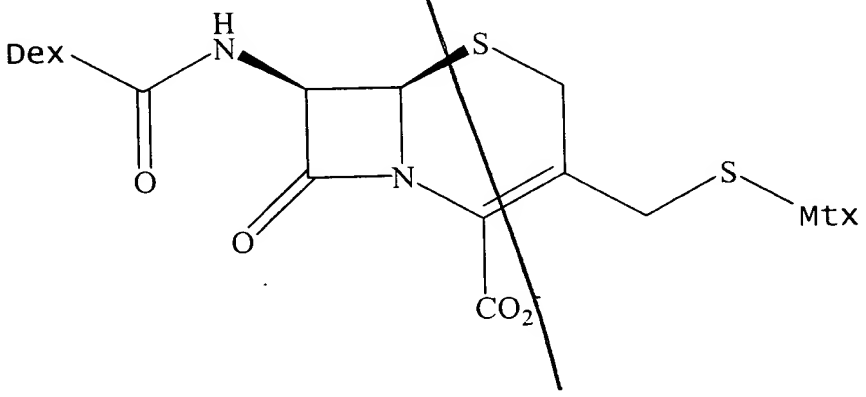
94. The compound of claim 91, having the formula:

Mtx-Y-H2.

95. The compound of claim 91, having the formula:

Dex-Y-Mtx.

96. The compound of claim 95, having the formula:



97. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 100 mM.

98. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 10 mM.

99. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 1 mM.

100. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 100 μM.

101. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 10 μM.

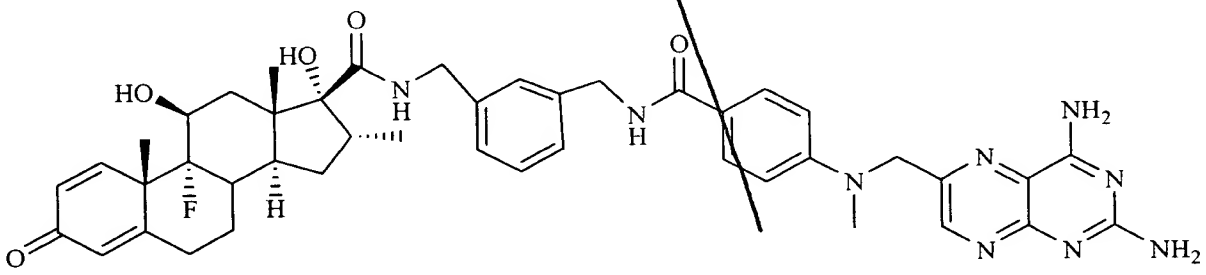
102. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 1 μM.

103. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 100 nM.

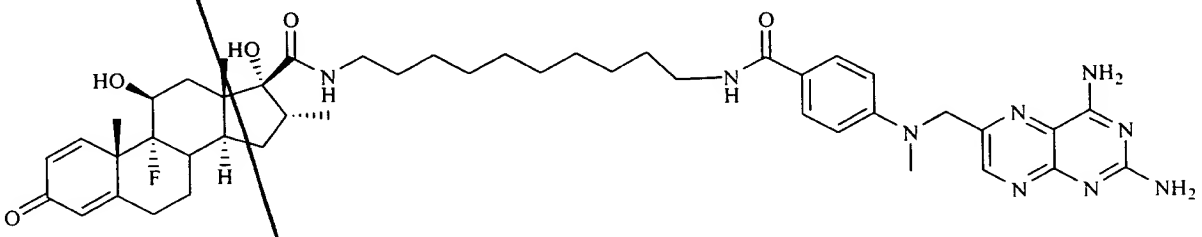
104. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 10 nM.

105. The compound of claim 91, wherein H2 is capable of binding to a receptor with a IC50 of less than 1 nM.

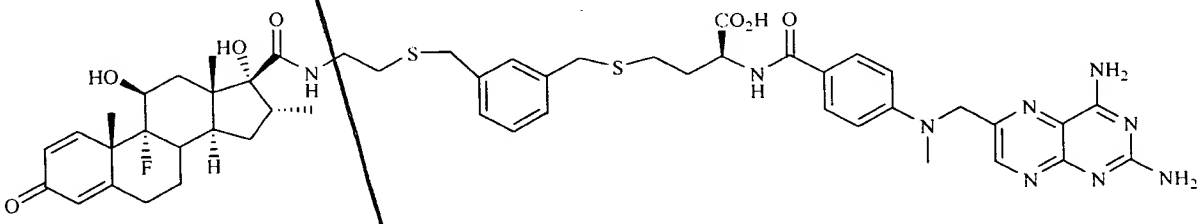
106. The compound of claim 95 having the formula:



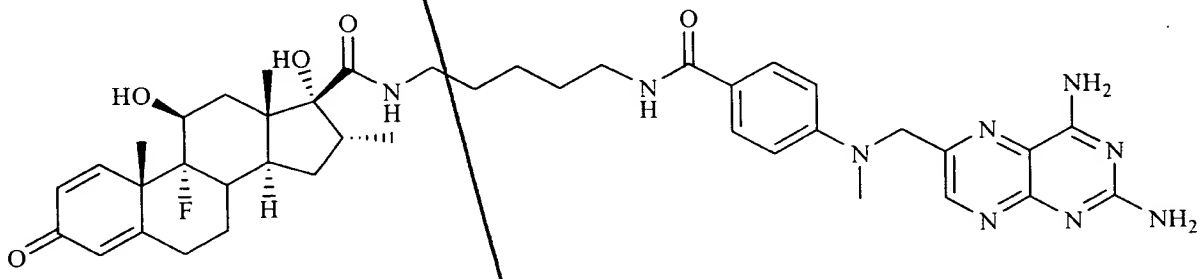
107. The compound of claim 95 having the formula:



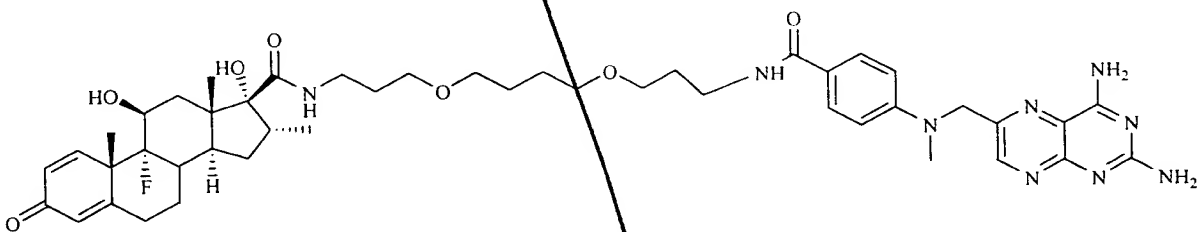
108. The compound of claim 95 having the formula:



109. The compound of claim 95 having the formula:



110. The compound of claim 95, having the formula:



111. A complex between the compound of claim 91 and a fusion protein which comprises a binding domain capable of binding to methotrexate, wherein H1 of the compound binds to the binding domain of the fusion protein.

112. The complex of claim 111, wherein the binding domain is that of the dihydrofolate reductase (DHFR).

113. The complex of claim 111, wherein H1 is capable of binding to the binding domain of the fusion protein with an IC50 of less than 100 nM.

114. The complex of claim 111, wherein H1 is capable of binding to the binding domain of the fusion protein with an IC50 of less than 10 nM.

115. The complex of claim 111, wherein H1 is capable of binding to the binding domain of the fusion protein with an IC50 of less than 1 nM.

116. The complex of claim 111, wherein H1 is capable of binding to the binding domain of the fusion protein with an IC50 of less than 100 pM.

117. The complex of claim 111, wherein H1 is capable of binding to the binding domain of the fusion protein with an IC50 of less than 10 pM.

118. The complex of claim 111, wherein H1 is capable of binding to the binding domain of the fusion protein with an IC50 of less than 1 pM.

119. The complex of claim 111, wherein the fusion protein is DHFR-(DNA-binding domain).

120. The complex of claim 111, wherein the fusion protein is DHFR-LexA.

121. The complex of claim 111, wherein the fusion protein is DHFR-(transcription activation domain).

122. The complex of claim 111, wherein the fusion protein is DHFR-B42.

123. A complex between the compound of any one of claims of claims 106-110, and the fusion protein DHFR-LexA.

124. The complex between the compound of any one of claims of claims 106-110, and the fusion protein DHFR-B42.

125. A cell comprising the complex of claim 111.

126. The cell of claim 125, where the cell is selected from the group consisting of yeast, bacteria or mammalian.

127. The cell of claim 125, where the cell is selected from the group consisting of *S. cerevisiae*, and *E. coli*.

128. A method of dimerizing two fusion proteins inside a cell using the compound of claim 91, comprising the steps of a) providing a cell that expresses a first fusion protein which comprises a binding domain that binds to H1 and second fusion protein which comprises a binding domain that binds to H2, and b) contacting the compound of claim 91 with the cell so as to dimerize the two fusion proteins.

129. The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-(DNA-binding domain).

130. The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-LexA.

131. The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-(transcription activation domain).

132. The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-B42.

133. A method for identifying a molecule that binds a known target in a cell from a pool of candidate molecules, comprising:

(a) covalently bonding each molecule in the pool of candidate molecules to a methotrexate moiety or an analog of methotrexate to form a screening molecule;

(b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the known target, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;

(d) selecting which cell expresses the reporter gene; and

(e) identifying the small molecule that binds the known target.

134. The method of claim 133, wherein the cell is selected from the group consisting of insect cells, yeast cells, mammalian cell, and their lysates.

135. The method of claim 133, wherein the first or the second fusion protein comprises a transcription module selected from the group consisting of a DNA binding protein and a transcriptional activator.

136. The method of claim 133, wherein the molecule is obtained from a combinatorial library.

137. The method of claim 133, wherein the steps (b)-(e) of the method are iteratively repeated in the presence of a preparation of random small molecules for competitive binding with the hybrid ligand so as to identify a molecule capable of competitively binding the known target.

138. A method for identifying a protein target to which a molecule is capable of binding, comprising:

(a) providing a screening molecule comprising a methotrexate moiety or an analog of methotrexate covalently bonded to a ligand which has a specificity for an unknown protein target;

(b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the unknown protein target, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;

(d) selecting which cell expresses the reporter gene; and

(e) identifying the unknown protein target.

139. The method of claim 138, wherein the unknown protein target is encoded by a DNA from the group consisting of genomicDNA, cDNA and syntheticDNA.

140. The method of claim 138, wherein the ligand has a known biological function.

Add B'